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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,782	11/27/2006	Mark L. Boys	PC28082A	6061

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PATENT DEPARTMENT, Bld 114 M/S 114
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EXAMINER	
MCDOWELL, BRIAN E	
ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
04/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/583,782	BOYS ET AL.	
	Examiner	Art Unit	
	BRIAN MCDOWELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/26/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13, 16, and 17* is/are pending in the application.

4a) Of the above claim(s) *16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

/BEM/

DETAILED ACTION

Status of Claims

Claims 1-13, 16, and 17 are pending in the instant application.

Status of Non-Statutory Use Claims

Applicant's cancellation of claims 14 and 15, see Remarks, filed 2/26/2009, with respect to the Non-Final Office Action mailed 11/26/2008, has been fully considered.

Status of Claim Objection

Applicant's amendment of claim 13, see Remarks, filed 2/26/2009, with respect to the objection set forth in the Non-Final Office Action mailed 11/26/2008, has been fully considered and the objection has been overcome.

Status of Specification

Applicant's arguments, see Remarks, filed 2/26/2009, with respect to the objection set forth in the Non-Final Office Action mailed 11/26/2008, have been fully considered and the objection has been overcome.

Status of Claims 16-17

Newly submitted claims 16 and 17 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The newly presented claims are drawn to methods of treatment. The claims as originally filed were directed to compounds.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for

prosecution on the merits. Accordingly, claims 16 and 17 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Status of Rejections

35 USC § 112 (2nd Paragraph)

The rejection of claims 1-11 and 13 is still maintained.

Applicant's amendment of claim 1, see Remarks, filed 2/26/2009, with respect to the rejection set forth in the Non-Final Office Action mailed 11/26/2008, has been fully considered but is not found persuasive. The term "hydrido" still appears in claim 1 and its respective dependent claims.

35 USC § 112 (1stParagraph)

Applicant's amendment of claim 1 (in reference to the 112 rejection of claims 1-3) see Remarks, filed 2/26/2009, with respect to the rejection set forth in the Non-Final Office Action mailed 11/26/2008, has been fully considered and the rejection has been overcome.

New Objections and Rejections

Specification

The disclosure is objected to because of the following informalities: In all occurrences the term "hydrido" should be replaced with "hydrogen" throughout the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds and/or compositions where X = O, R^a = R^c = H, R^d = 3-piperidinyl, and R^b = a 6-membered aryl ring that may be substituted with hydrogen, -OR^3 (wherein R^3 = hydrogen, C_{1-6} alkyl, C_{5-7} cycloalkyl, benzyl, -CH_2(C_{3-7} cycloalkyl), and C_{3-12} aryl), C_{1-6} alkyl, C_{5-7} cycloalkyl, benzyl, -CH_2(C_{3-7} cycloalkyl), and C_{3-12} aryl, halo, 3- to 12-membered heterocycloalkyl, 3- to 12-membered heterocycloalkenyl, and 3- to 12-membered heteroaryl, does not reasonably provide enablement for the other thousands of compounds that applicant is claiming. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Pursuant to In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444. Analysis is described below:

(A) Breadth of claims: The formula I is drawn to a myriad of substituents that vary independently and lead to compounds of a wide variety of structures. These compounds encompass molecules that widely vary in the physical and chemical properties such as size, molecular weight, acidity, basicity, and properties that are known in the art to greatly influence pharmacokinetic and pharmacodynamic parameters, not to mention the ability to productively bind to claimed biological target molecules. The claims cover compounds easily in the millions given the number of possible rings, ring systems covered by the claims' scope along with varying choices for remaining variables; thus the claims are very broad.

(B) The nature of the invention: Substituted pyrazinones possessing piperidines at the 1-position for treating inflammatory diseases.

(C) State of the Prior Art: Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task.

In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)" Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

(D) Skill of those in the art: The level of skill in the art is high.

(E) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(F) Direction or Guidance: Little guidance or direction is provided by applicant in reference to making compounds other than those with the variables mentioned previously. The presence of various bulky heterocyclic or carbocyclic rings attached to the compound's core may be chemically incompatible with the method of use embraced

in the instant claims. Specification offers no teachings or suggestion as to how to make and use these compounds. Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.";

(G) Working Examples: The compound core depicted with specific substituents represent a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed. Applicant has provided no working examples of any compounds where the compound of formula I did not contain the variables previously mentioned above in the present application.

The specification gives some *in vitro* test results on IKK-2 inhibitory effects of a limited number of preferable compounds, however it is too homogeneous to provide a clear evaluation of which moieties attached to the compound's core out of the many claimed might affect potency to a large or small degree. The pharmaceutical art is unpredictable and target compounds need to be individually assessed for viability. Extremely broad generalizations as found in the instant claims are in contradiction with the basis of quantitative structure-activity-relationship (QSAR).

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula

of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

(H) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome. Applicant fails to provide guidance and supporting information for how to make and/or use the thousands of other compounds which are encompassed by the claims, therefore undue experimentation would be expected.

Due to the level of unpredictability in the art, the very limited guidance provided, and the lack of working examples, the applicant has shown lack of enablement. MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Conclusion

No claims are allowed.

Claim 12 is objected to as being dependent upon a rejected or objected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Reasons for Allowance

Claim 12 encompass species that possess novel heterocyclic (3-piperidinyl) and phenyl moieties at variables R^d and R^b, respectively

The limitations listed supra represent the limitations that are not taught or fairly suggested by the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN MCDOWELL whose telephone number is (571)270-5755. The examiner can normally be reached on Monday-Thursday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/B. M./
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, AU 1624